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Manganese-catalyzed base-free addition of saturated nitriles to unsaturated nitriles by template catalysis†

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The coupling of mononitriles into dinitriles is a desirable strategy, given the prevalence of nitrile compounds and the synthetic and industrial utility of dinitriles. Herein, we present an atom-economical approach for the heteroaddition of saturated nitriles to α,β- and β,γ-unsaturated mononitriles to generate glutaronitrile derivatives using a catalyst based on earth-abundant manganese. A broad range of such saturated and unsaturated nitriles were found to undergo facile heteroaddition with excellent functional group tolerance, in a reaction that proceeds under mild and base-free conditions using low catalyst loading. Mechanistic studies showed that this unique transformation takes place through a template-type pathway involving an enamido complex intermediate, which is generated by addition of a saturated nitrile to the catalyst, and acts as a nucleophile for Michael addition to unsaturated nitriles. This work represents a new application of template catalysis for C–C bond formation.

Introduction

Nitriles are fundamental building blocks in organic synthesis, and are ubiquitous in natural products, biologically active compounds and pharmaceuticals.[1] Moreover, they are invaluable intermediates in present-day chemical industry, used for the synthesis of amines, imines, amides, aldehydes, ketones, and carboxylic acid derivatives.[2,3] Dinitriles are employed as primary precursors in the polymer industry, but are also used as building blocks for fine chemicals.[4] For instance, the linear dinitrile glutaronitrile is an attractive intermediate for the synthesis of substituted N-heterocycles, such as piperidines, pyridines, and other amine derivatives.[5] Furthermore, dinitrile compounds can be easily converted into diamines, diesters and diamides, as well as lactones, lactams, and cyclic imides.[6] Nevertheless, the synthesis of dinitriles, including glutaronitrile and its substituted variants, normally requires the use of toxic cyanide or multistep processes that involve harsh conditions.

Michael addition, which is a well-known type of conjugate addition reaction,[7] is an established synthetic tool for generating C–C bonds.[8] Nevertheless, this kind of reaction typically requires the *in situ* generation of carbon nucleophiles (Michael donors) through the use of strong bases, which may be incompatible with sensitive functional groups and can lead to undesired side products.[9] Transition-metal-catalyzed variants of Michael-type reactions have been receiving growing attention due to their excellent selectivity and efficiency.[10] Catalytic base-free Michael additions involving nitriles were pioneered in the late 1980's by Murahashi and coworkers, who reported a series of ruthenium-catalyzed reactions of activated nitrile nucleophiles featuring acidic α-methylene and α-methine groups (*i.e.*, active methylene nitriles).[11] Since then, other examples of transition-metal-mediated Michael-type reactions of activated nitriles have been reported.[12] However, these processes required the use of bases or other additives, and were conducted at high temperatures. In 2013, we made our first contribution to this field, when we reported the catalytic Michael addition of benzyl cyanides to α,β-unsaturated carbonyl compounds, promoted by a pincer-type rhenium complex capable of metal–ligand cooperation (MLC), and carried out under base-free and mild conditions.[13]

The phenomenon of MLC, wherein both the metal center and ligand of a given complex are directly involved in bond activation, has opened new opportunities for selective activation of chemical bonds and has led to the discovery of new catalytic reactions that are atom-economical and environmentally-benign.[14] Significant advances in this field have been achieved by our group, primarily using transition metal complexes of pyridine-based PNP- and PNN-type pincer ligands that exhibit aromatization/dearomatization of the pincer backbone, thereby enabling the cleavage of strong chemical bonds.[14,15] Such was the reactivity of the aforementioned rhenium complex, which bears

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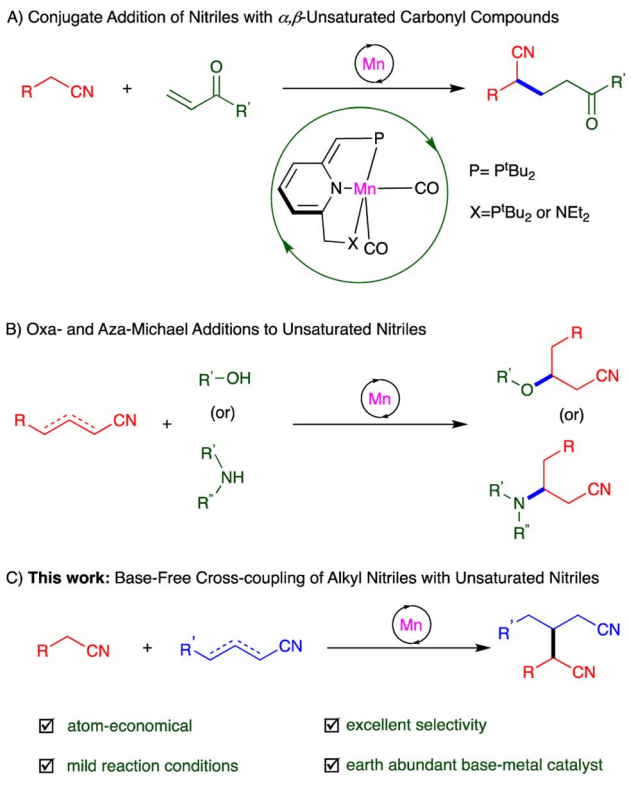
a PNP-type ligand and can activate the nitrile C≡N bond *via* reversible C–C coupling with the pincer backbone and simultaneous M–N coordination to the metal center.[13] The activated nitrile was found to be susceptible to electrophilic attack, either at its nitrogen or α-carbon atom, while the metal-pincer framework serves as an anchor, or template, for the nitrile substrate. This mode of activation, which we have termed "template catalysis", has enabled the catalytic substitution of nitriles at their α-positions.[16] Otten, de Vries and coworkers have also developed similar nitrile-activating systems employing pyridine-based PNP- and PNN-ruthenium pincer complexes.[17]

The application of earth-abundant transition metal catalysts in organic synthesis has been gradually expanding, in light of the high natural prevalence and low cost of these elements, as compared to noble metals – the long-established workhorses of catalysis – like the abovementioned ruthenium.[18,19] Manganese, a widely-used, inexpensive base metal, caught our attention nearly a decade ago, and we have since developed a series of PNP- and PNN-type complexes of this metal, which have shown unique catalytic activity based on MLC.[19] This includes template catalysis, which allowed us to accomplish a variety of new transformations involving nitriles, namely, Michael addition of unactivated nitriles to α,β-unsaturated carbonyl compounds,[16] oxa- and aza-Michael additions to unsaturated nitriles,[20] and hydration and α-deuteration of nitriles[21] (Scheme 1A and B).

Michael additions are typically carried out using stoichiometric amounts of strong bases, which are necessary for generating Michael donors *in situ*, but these bases are incompatible with many functional groups, as noted above.[10,12,22] Moreover, the electrophilic addition partners (Michael acceptors) used in such reactions have thus far been largely limited to α,β-unsaturated ketones, esters, amides and nitro compounds.[10] By contrast, α,β- and β,γ-unsaturated nitriles have rarely been reported as Michael acceptors, because such nitriles are prone to side reactions like polymerization and self-addition.[9,17b] Hence, directly using unsaturated nitriles for selective C–C bond formation *via* Michael addition reactions is a highly challenging task. Herein, we report the synthesis of glutaronitriles through direct addition of unactivated saturated nitriles to α,β- and β,γ-unsaturated nitriles, catalyzed by a PNP-manganese pincer complex under very mild, neutral conditions (Scheme 1C). This catalytic system, which operates in the absence of base, was shown to preserve base-sensitive functional groups, and afforded a variety of dinitriles in generally good to excellent selectivity and yield. To the best of our knowledge, such base-free catalytic heteroaddition of saturated nitriles to unsaturated ones to generate dinitriles has not been previously documented.

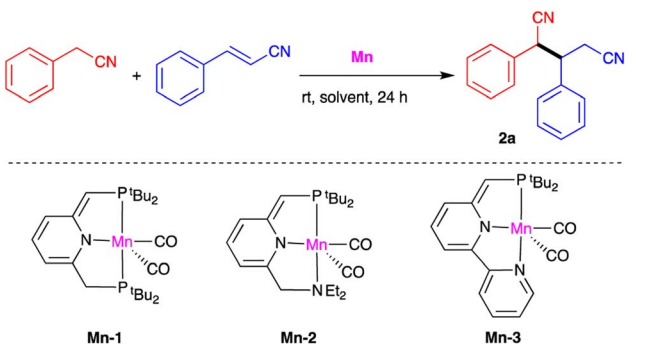
Results and discussion

Our investigation of catalytic nitrile heteroaddition began with a 1 : 1 mixture of benzyl cyanide and cinnamonitrile as model substrates, and the manganese complexes **Mn-1**, **Mn-2** and **Mn-3** as potential catalysts (Table 1). Using 0.5 mol% of **Mn-1** and THF as solvent, the corresponding dinitrile product **2a** was



Scheme 1 Addition reactions involving nitriles promoted by manganese pincer complexes through template catalysis.

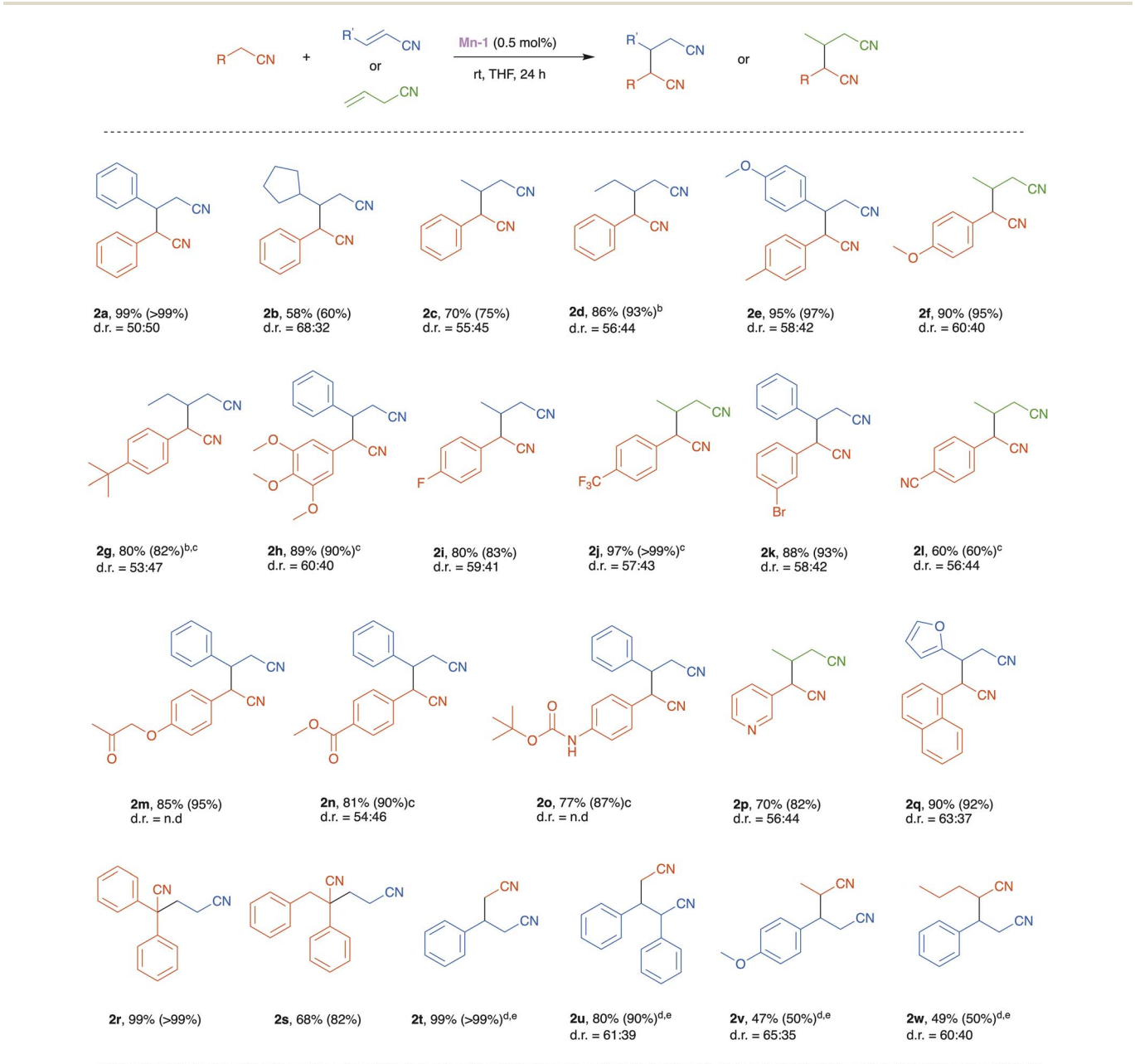
Table 1 Optimization of catalytic reaction conditions[a]



Entry	Catalyst	Solvent	Conversion[b]	Yield[c]
1	**Mn-1** (0.5 mol%)	THF	>99	99
2	**Mn-1** (0.3 mol%)	THF	80	76
3	**Mn-1** (0.5 mol%)	Benzene	78	76
4	**Mn-2** (0.5 mol%)	THF	80	80
5	**Mn-3** (0.5 mol%)	THF	72	70
6[d]	**Mn-1** (1 mol%)	THF	>99	99
7	—	THF	—	—

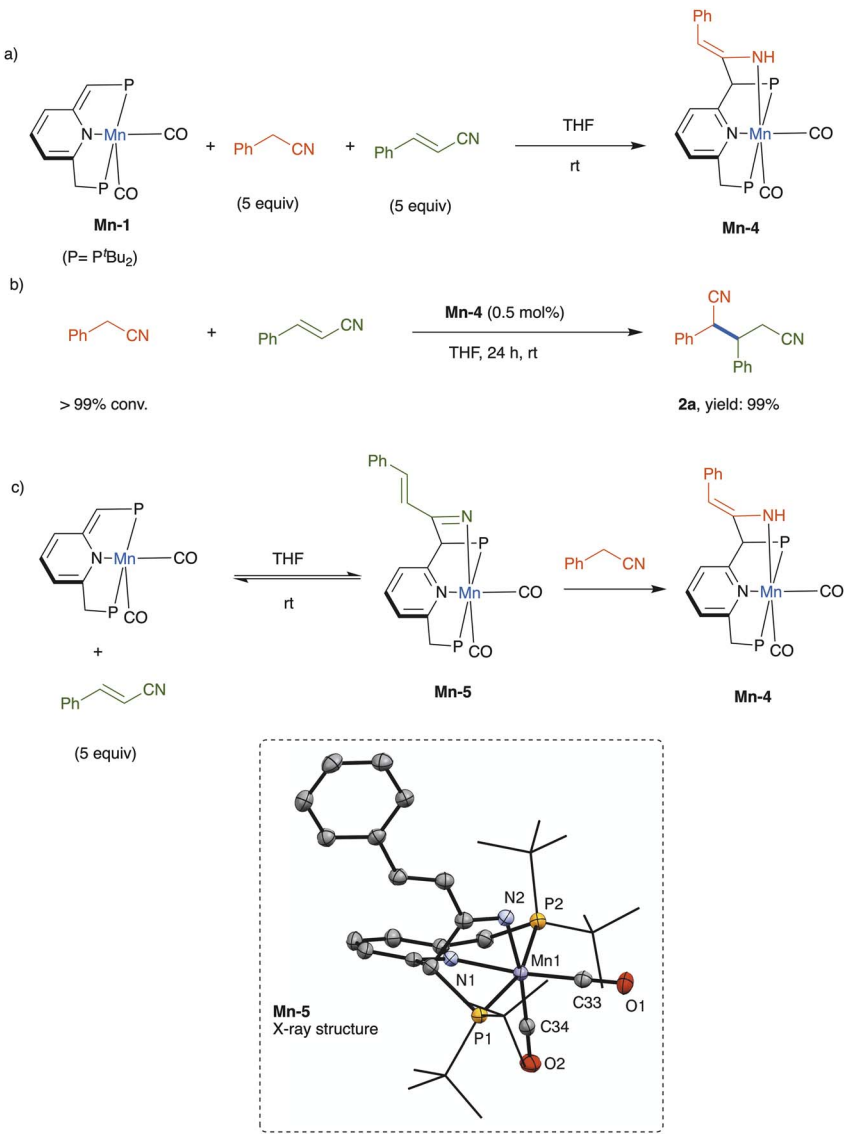
[a] Reaction conditions: benzyl cyanide (0.3 mmol), cinnamonitrile (0.3 mmol), solvent (1 mL), catalyst (loading as indicated), stirred at room temperature for 24 h. [b] Conversion of benzyl cyanide was determined by GC analysis, using mesitylene as internal standard. [c] Yield of **2a** was determined for the isolated compound after column chromatography. [d] 0.6 mmol (2 equiv.) of cinnamonitrile was used.

obtained in quantitative yield after 24 h at room temperature (Table 1, entry 1). Gas chromatographic (GC) analysis indicated that this dinitrile comprised a 1 : 1 mixture of diastereomers. Reducing the catalyst loading to 0.3 mol% decreased conversion to 80% and the isolated yield to 76% under otherwise identical conditions (entry 2), and very similar results were obtained when THF was replaced with benzene (entry 3). Complexes **Mn-2** and **Mn-3** were both found to catalyze the addition reaction, but were less effective than **Mn-1** (entries 4 and 5). It should be noted that using excess cinnamonitrile (2 equiv. *vs.* benzyl cyanide) did not result in double addition, and the single-addition product **2a** was the only observed product, isolated in 99% yield (entry 6). Finally, a control experiment was carried out in the absence of catalyst, but no product was obtained, clearly indicating the critical role of the catalyst (entry 7).

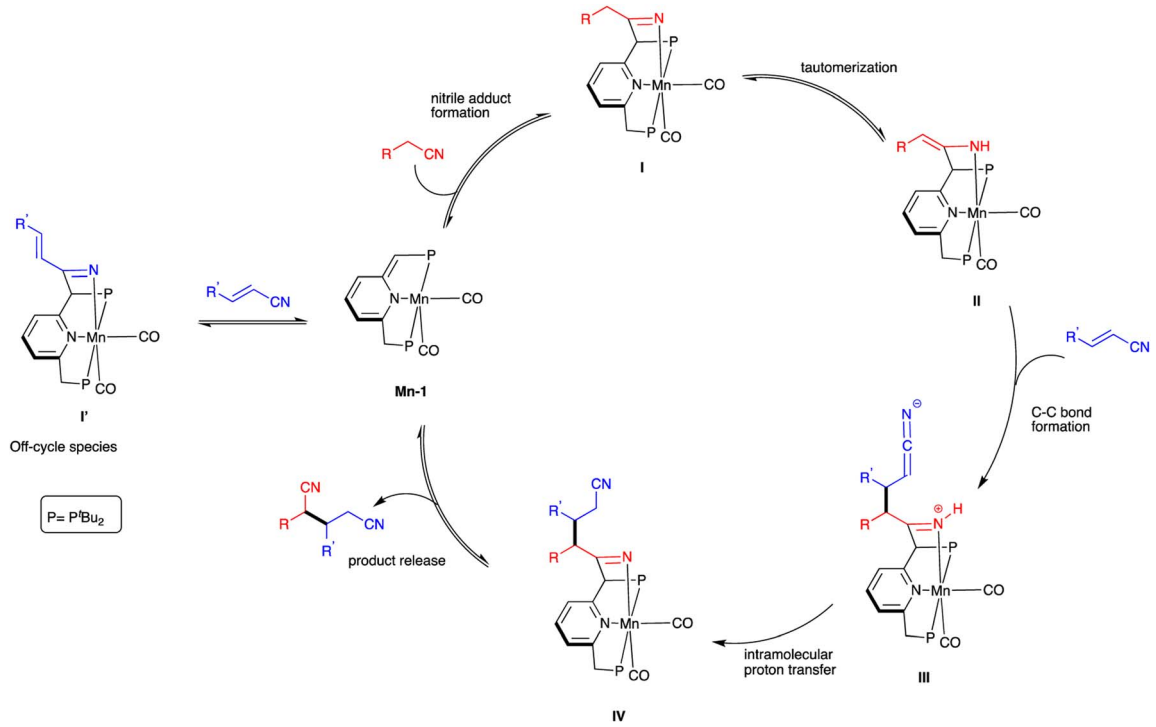


Scheme 2 Substrate scope of the manganese-catalyzed base-free heteroaddition of nitriles. [a]Reaction conditions: saturated nitrile (0.3 mmol), unsaturated nitrile (0.3 mmol), THF (1 mL), **Mn-1** (0.5 mol%), stirred at room temperature for 24 h. Reaction yields correspond to the pure isolated products. Values in parentheses are the conversions of the saturated nitrile substrates, as determined by GC analysis using mesitylene as internal standard. [b]Reaction performed without solvent. [c]2 mol% of **Mn-1** was used. [d]**Mn-1** (5 mol%), saturated aliphatic nitrile (1 mL) and unsaturated nitrile (0.3 mmol) were stirred at room temperature for 48 h. [e]The value in parentheses is the conversion of the vinyl nitrile, as determined by GC analysis using mesitylene as internal standard. The diastereoisomeric ratios (d.r.) noted for the various products were determined by GC or NMR spectroscopic analysis.

With the optimized reaction conditions in hand, we set to explore the substrate scope of our catalytic nitrile hetero-addition system (Scheme 2; **2a** is duplicated from Table 1 for comparative purposes). Reaction of benzyl cyanide with alkyl-substituted acrylonitrile derivatives, namely, *trans*-3-cyclopentyl-acrylonitrile and crotononitrile, afforded the corresponding products, **2b** and **2c**, in moderate to good yields (Scheme 2). Benzyl cyanide was also coupled with 2-pentenenitrile, but in the absence of solvent, giving dinitrile **2d** in excellent yield, thereby demonstrating the efficiency of the catalytic system under solvent-free conditions. Furthermore, benzyl cyanides bearing various electron donating and withdrawing substituents on their arene rings were coupled with different unsaturated nitriles, affording the corresponding products, **2e–l**, in good to excellent yields. This indicates that the present catalytic system tolerates these substituents, and this is particularly notable for the halogen and cyano functionalities. Moreover, these experiments show that catalyst **Mn-1** can promote both the isomerization of allyl cyanide and its subsequent conjugate addition to saturated nitriles (**2f**, **2j** and **2l**). Importantly, base-sensitive functional groups, namely, ketone, ester, and amide, were also tolerated, and the corresponding dinitrile products **2m–o** were isolated in good yields. An N-heterocyclic saturated nitrile underwent smooth hetero-addition, using allyl cyanide as its partner, to furnish dinitrile **2p** in 70% yield. Similarly, an O-heterocyclic α,β-unsaturated nitrile, 2-furanacrylonitrile, was coupled with 1-naphthylacetonitrile to give the desired product **2q** in 90% yield. The reaction of α-substituted benzyl cyanides with acrylonitrile proceeded efficiently to afford the desired products **2r** and **2s** in 99% and 68% yield, respectively. Lastly, we examined the highly challenging application of unactivated aliphatic nitriles as substrates in our catalytic system. Under the optimized catalytic conditions, acetonitrile reacted with cinnamonitrile to give the



Scheme 3 Mechanistic studies.



Scheme 4 Proposed mechanism of nitrile heteroaddition catalyzed by Mn-1.

corresponding product **2t** in low yield (<20%). However, employing acetonitrile as solvent, instead of THF, and increasing the catalyst loading to 5 mol%, enabled us to achieve high to quantitative product yields (**2t** and **2u**). It should be noted that when the reaction of acetonitrile with cinnamonitrile was repeated under the same conditions, but with the manganese catalyst replaced by an equimolar amount of the strong base KO^{t}Bu, poor results were obtained (8% conversion, 5% yield of product **2t**), thereby highlighting the nitrile coupling efficiency of **Mn-1** relative to general base catalysis. Other unactivated nitriles, *i.e.*, propionitrile and pentanenitrile, were coupled with vinyl nitriles, using **Mn-1** under similar conditions, to afford products **2v** and **2w** in 47% and 49% yield, respectively (Scheme 2).

The underlying mechanism of nitrile addition catalyzed by complex **Mn-1** was probed through stoichiometric experiments (Scheme 3). A competition experiment was performed, wherein this catalyst was treated with an equimolar mixture of benzyl cyanide and cinnamonitrile, each at 5 equiv. per catalyst, in THF at room temperature (Scheme 3a). Interestingly, only benzyl cyanide reacted productively with the dearomatized complex, affording the respective rearomatized enamido complex **Mn-4**, whereas no cinnamonitrile complex, nor derivative thereof, was observed (see ESI†). This enamido complex has already been fully characterized, including X-ray crystallographic and density functional theory analyses, as part of our previous work on conjugate additions involving nitriles.[16] In the present work, when independently-prepared **Mn-4** was employed as catalyst, benzyl cyanide and cinnamonitrile were coupled to quantitatively give dinitrile **2a** (Scheme 3b), thereby implying that the enamido complex is an intermediate in this addition reaction.

The aforementioned competition experiment showed that **Mn-1** reacts preferentially with benzyl cyanide, rather than cinnamonitrile. This is due to the higher thermodynamic stability of the generated enamine complex, which cannot be formed in the case of cinnamonitrile.[23] However, in the absence of benzyl cyanide, this complex reacted with 5 equiv. of cinnamonitrile in THF to afford a new complex, the ketimido adduct **Mn-5** (Scheme 3c), which was structurally identified by NMR spectroscopy and X-ray crystallography (see ESI† for full details). In THF solution, **Mn-5** exists in equilibrium with **Mn-1** and free cinnamonitrile, and addition of benzyl cyanide (5 equiv.) leads to quantitative formation of complex **Mn-4** within minutes at room temperature (Scheme 3c).

A plausible catalytic cycle for nitrile heteroaddition by **Mn-1** is proposed (Scheme 4), based on the above experimental observations and previous mechanistic studies involving this complex.[16,20,21] Initially, the saturated nitrile adds across the dearomatized metal-ligand framework of **Mn-1** to generate the rearomatized ketimido intermediate **I**, which undergoes facile tautomerization to the thermodynamically more stable enamido intermediate **II**. The ketimido species **I′**, which forms reversibly upon reaction of **Mn-1** with the unsaturated nitrile, is likely an off-cycle species that is not directly involved in the catalytic mechanism. Intermediate **II** reacts with the unsaturated nitrile through a Michael-type addition, leading to C–C bond formation between the two species and generating the formally zwitterionic intermediate **III**. This, in turn, undergoes proton transfer from the N–H bond of the coordinated ketimine group to the dangling ketenimide fragment, affording intermediate **IV**. Finally, the dinitrile product is released from this intermediate, thereby

regenerating the dearomatized complex **Mn-1** and closing the catalytic cycle.

Conclusions

In summary, we have presented the first example of transition-metal-catalyzed heteroaddition of benzylic and aliphatic nitriles to α,β- and β,γ-unsaturated nitriles to generate glutaronitrile derivatives. The resulting dinitrile compounds represent valuable intermediates in N-heterocycle synthesis and the polymer industry. Mechanistic investigations demonstrated the selective activation of a saturated nitrile over an unsaturated one. Moreover, the synergistic cooperation between the dearomatized PNP–Mn complex and saturated nitriles allows the generation of an enamido–manganese species, which is a key mechanistic intermediate. The new synthetic protocol outlined above provides facile means of nitrile heteroaddition at room temperature under base-free conditions, thereby allowing access to dinitrile compounds in an atom-economical, environmentally benign fashion.

Data availability

The authors declare that all supporting data are available in the ESI† and from the corresponding author upon request.

Author contributions

D. M. and S. T. conceived and directed the project and designed the experiments. S. T. performed all of the experiments and analyzed their results. Y. D.-P. carried out the crystallographic studies. M. M. provided insightful discussions. D. M., S. T. and M. M. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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23 Our previous work has shown that the reaction of **Mn-1** with benzyl cyanide readily forms enamido complex **Mn-4**, wherein the enamido moiety is stabilized by conjugation to an aromatic ring (see ref. 16). We have also demonstrated that propionitrile reacts with **Mn-1** to predominately give the corresponding ketamido complex (imine intermediate), rather than an enamido one (enamine intermediate), because propionitrile cannot stabilize the latter through conjugation. Thus, our previous results clearly indicate that the complex bearing the imine intermediate is less stable, and is in equilibrium with the dearomatized manganese complex **Mn-1** and free nitrile.